

# Chemical Regulation

It is human nature to want to protect our children from harm. Toys, car seats, sports equipment—all are designed with a child's safety in mind. Those same children, however, have been often overlooked in two critical research areas: the effects of exposure to chemicals and guidelines for prescription medications. Environmental exposure standards have usually been set according to research on adults, and prescription medications are primarily designed for grown-ups as well. This has led to a shortage of concrete information on how children's developing bodies respond to potential hazards in their environment and to the drugs they may take.

"The single most important point I would like to make is that children are not little adults," said E. Ramona Trovato, director of



## In Search of a Better Fit

the Office of Children's Health Protection of the U.S. Environmental Protection Agency (EPA), before a congressional subcommittee in May. In order to learn more about children's health needs with respect to their environments, she added, "we [the EPA] support and encourage extensive, coordinated research to establish the scientific basis for our risk assessments and regulatory decision making."

From the womb to the schoolyard, children may be exposed to a wide array of environmental health contaminants, including chemicals, lead, pesticides, fertilizers, ozone, and asbestos. Their young metabolisms also affect how they may absorb, metabolize, excrete, and respond to psychotropic drugs, anesthesia, and medications for conditions such as asthma, epilepsy, severe pain, gastrointestinal problems, and allergic reactions. Because children are often

overlooked in clinical trials, many are prescribed such drugs off-label, meaning they receive treatments that were not designed for that particular use or age group. Although the practice is not illegal, little is known about the efficacy and safety of drugs used in this way.

"At one time, it wasn't considered ethical to study children in clinical trials because children can't really give informed consent. They can't really understand the risks and benefits of participating in a trial," says Dianne Murphy, associate director for pediatrics at the Center for Drug Evaluation and Research of the U.S. Food and Drug Administration (FDA). There were also technical problems, she says, one of which was the relatively large volume of blood samples frequently needed for trials, which were difficult to obtain from children because of the discomfort such tests can cause. For these and other reasons, children have seldom been enrolled in either chemical research studies or pharmaceutical drug development trials.

#### Filling the Data Gap

Per pound of weight, children drink more water, eat more food, and breathe more air than adults, potentially placing them at greater risk for adverse effects from environmental exposures, says William Farland, director of the EPA National Center for Environmental Assessment. "We also know that they have windows of vulnerability," he says, meaning that there are periods in a child's earliest development in which any damage that may occur can have lifelong effects.

In April 1998, Vice President Al Gore called for the EPA "to review and report on what new testing may be needed to assess the special impact industrial chemicals may have on children." In August 1999, the EPA announced its plans to develop a Voluntary Children's Chemical Evaluation Program, which would evaluate chemicals with children's health concerns. Once appropriate chemicals are identified as having potential negative effects on children, chemical producers will be asked to voluntarily conduct any tests that might confirm such suspicions. The EPA is also investigating ways to run toxicological studies of this kind.

Early on in the EPA proposal's public comment period, Jerome A. Paulson, a physician at the George Washington University Schools of Medicine and Public

Health, issued a response on behalf of the Children's Environmental Health Network (CEHN), a public interest organization devoted to improving children's health. Paulson argued that rather than wait until chemicals are identified for testing—a potentially lengthy process—the EPA should quickly identify and test chemicals that are clearly a high priority, "those in which the evidence is quite clear

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**—Daniel Swartz**

that our children are highly exposed to them." These might be chemicals in consumer products, pesticides, drinking water, or breast milk, or those that are inadvertently brought home by parents from their place of work.

As currently written, the Voluntary Children's Chemical Evaluation Program's proposed test battery does not include acute eye and dermal irritation studies or dermal sensitization studies, according to Paulson, because the most relevant routes of exposure are likely to be oral and inhalational. However, Paulson and the CEHN are concerned that eliminating dermal testing might overlook exposure from substances such as soaps, shampoos, and diaper rash creams, for example, as well as from carpets, clothing, and water. A newborn's skin, he says, is more permeable than that of an older child and can absorb chemicals that result in illness.

"On one level, we certainly have a lot more information than we had 10 years

ago," adds Daniel Swartz, executive director of the CEHN. "The good news is that there's a recognition that having information about adults doesn't mean we know what's happening with kids. In the past, you could have listed all of the relevant articles in a brief bibliography. But there are still major problems today. What's hindering better knowledge is the lack of good data about what kids are actually exposed to in their lives. It will be very hard to get a good handle on why they get diseases if you don't know what they interact with."

Concern has been growing about the prevalence of pesticides and other chemicals that children are exposed to in a variety of ways, at home, via their toys, and in the schoolyard. Chemicals used near schools to control everything from bumblebees to mold include pesticides such as organophosphates, chlorpyrifos, and synthetic pyrethroids. Certain children's toys are manufactured with chemical plasticizers called phthalates that have been linked to adverse health effects such as liver and kidney damage and testicular problems. And many, if not most, of these chemicals are used with little understanding of their potential effect on children's health.

Traditionally data have come from tests done on animals in which the results are then extrapolated to humans. Although food-use pesticide registrations require developmental toxicity studies and generational reproduction studies that are used to evaluate potential pre- and postnatal toxicity, extrapolating from animal bioassays is not a perfect method. For example, says Lynn Goldman, an adjunct professor in the Department of Health Policy and Management at the Johns Hopkins School of Hygiene and Public Health in Baltimore, Maryland, "Prenatal and perinatal are the times when cells are rapidly growing and differentiating. We know that many childhood cancers are of primitive cell origin. If you wait to test, you miss periods where immune and metabolic systems are immature. Moreover, if genetic changes do occur, they can become permanent and result in increased cancer risk in adults."

#### Pharmaceuticals

Collecting data on children has challenged the pharmaceutical industry as well. In the

late 1970s, the American Academy of Pediatrics called for companies to perform clinical trials for children so that medications would feature labels that described dosing, usage, contraindications, and other warnings related specifically to children. The academy argued that it would be more ethical to include children in clinical trials than to continue uncontrolled experimenting on them by giving them off-label drugs. Without proper guidelines, pediatricians are forced to estimate dosing regimens.

"In general, two-thirds to three-quarters of the prescriptions pediatricians write for patients are off-label," says Murphy. "But you can't tell them that they can't prescribe off-label because you would cut off care to kids who need treatment. We don't want to deny access to children who need these therapies."

In 1994, the FDA published a rule requiring pharmaceutical companies to submit any available information on their products' potential use by children so that the labels could be updated. The response was disappointing, according to Murphy. Few companies had ever run clinical trials on children because the cost and complexity of conducting such studies had deterred them from making the investment.

However, the last few years have seen new impetus for running such trials. "Congress finally figured it out," says Murphy, "and said, 'Look, folks, if you really want them to study children, you'll need to offer an incentive.' They passed Section III of the Food and Drug Administration Modernization Act in 1997, which allowed pharmaceutical companies to obtain six more months of market exclusivity for a product if they would conduct pediatric drug trials. We've had a tremendous response to that."

One of the higher-profile medications used off-label today is Ritalin, a stimulant designed to treat attention disorders. Ritalin has been tested and approved for use in children six years old and above. However, in the 23 February 2000 issue of the *Journal of the American Medical Association*, researchers from Maryland and Oregon reported an acute increase in the number of preschoolers taking Ritalin as well as antidepressants (such as Prozac), antipsychotics, and clonidine (used to treat adult high blood pressure and insomnia in hyperactive children). The authors present data from 200,000 preschool-aged

children around the United States. "Controlled clinical studies to evaluate the efficacy and safety of psychotropic medications for preschoolers are rare," they report. "Because children's responses to medications are not necessarily similar to those of adults, systematic and careful outcome research specifically needs to be done for them." The report continues, "[T]he possibility of adverse effects on the developing brain cannot be ruled out. Active surveillance mechanisms for ascertaining subtle changes that the developing personality may undergo as a result of a psychotropic drug's impact on brain neurotransmitters should be developed."

In March, the Clinton administration initiated a campaign to address the issue of the increase in the use of such medications by very young children. As part of this

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**—JAMA, 23 February 2000**

effort, the FDA plans to develop new pediatric drug labeling information for psychotropic drugs used in young children, and work with the National Institute of Mental Health to ascertain research needs in this area, including a proposed nationwide study of Ritalin use in children under the age of six.

Conducting clinical trials on children has already yielded important results. For example, Versed, a medication designed to sedate and relax patients before operations, was commonly used for children although inadequate research had been done on its

effects on them. Although Roche Pharmaceuticals (the company that manufactures Versed) had already run extensive safety and efficacy clinical trials, the FDA requested additional tests on special pediatric populations including children with medical conditions that could be adversely affected by the medication. By observing the responses of pediatric patients in a hospital setting before, during, and after an operation, Roche was able to determine that obese children should be dosed according to their ideal body weight rather than their actual weight to avoid risk of an overdose. In addition, children with congenital heart disease should receive a lower dose or risk developing breathing difficulties. Without this knowledge, certain children had been placed at higher risk for serious side effects.

### **A Change in Thinking**

Concern over the effects of environmental and pharmaceutical agents in children is a worldwide issue. In an article in the 8 January 2000 issue of the *British Medical Journal*, researchers reported on the widespread use of unlicensed and off-label drugs in pediatric wards throughout Europe. In response to concern about the lack of information on the actual effects of such medications, the European Union (EU) is developing guidance on the clinical investigation of medicinal products in children that encourages pharmaceutical companies to test new products in children when clinically appropriate.

The EU also approved an emergency ban on certain plastic baby toys in December 1999. The EU feared that the phthalates used to soften the toys could harm babies by leaching out when infants teethe or suck on them.

It is clear that children in the United States and abroad are increasingly finding themselves in an environmental health research and drug development category of their own. Widespread pesticide use in the schoolyard, for example, and the growing use of psychotropic drugs in very young populations provide just a few compelling reasons for increasing the focus on testing chemicals for their impact on children's health. But the questions remain of who should do the testing and how it should be carried out.

**Rebecca Clay**